REMARKS

Reconsideration of this application is respectfully requested. Claims 1-30 are pending in the application. Claims 24-28 are withdrawn from consideration. Claims 1 and 5- 23 have been amended, in part to renumber the claims due to inadvertent inclusion of two claims originally designated as claim number 5, and in part to better clarify what Applicants believe to be the invention (claim numbers 1, 10 (originally 9) and 19 (originally 18)). New claims 29 and 30 have been added for consideration. Support for the amendments and the new claims can be found throughout the specification, but particularly on page 12, lines 7-9; page 15, lines 20-22; page 18, lines 1-2; page 25, lines 9-23; and in Figures 10 and 13A-B. Accordingly, if new claims 29 and 30 are entered, claims 1-23 and 29-30 are under consideration.

Applicants' representatives would like to express their sincere appreciation for the telephonic discussions held with Examiner Parkin on December 4, 2004 and on January 6, 2005 as related to the references submitted in support of Applicants' position that Stamatatos and Cheng-Mayer do not render the pending claims unpatentable under 35 U.S.C. 103(a). The summaries of both interviews are attached herewith. As noted in those conversations, while Applicants contend that the references submitted teach away from the Stamatatos and Cheng-Mayer reference, Examiner Parkin was not in agreement with Applicants and suggested that further claim amendments would be necessary to differentiate the present invention from the Stamatatos and Cheng-Mayer reference. Accordingly, and on this basis, Applicants have amended the claims to recite such differences and submit that the claims as currently amended place the application in condition for allowance.

Rejections Under 35 USC § 103(a)

Claims 1-23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Stamatatos and Cheng-Mayer (1998). This rejection is respectfully traversed.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior

art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 US 1 (1966). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion that the combination be made. In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987).

As previously set forth, the Examiner asserts that the teaching of the present application is directed toward SF162, a primary (PR), non-syncytium-inducing, macrophagetropic human immunodeficiency virus type 1 (HIV-1) clade B isolate which is resistant to antibody-mediated neutralization. Moreover, it was reported that deletion of the first or second hypervariable envelope gp120 region (VI or V2 loop, respectively) of this virus does not abrogate its ability to replicate in peripheral blood mononuclear cells and primary macrophages, nor does it alter its coreceptor usage profile. Furthermore, the mutant virus with the V1 loop deletion, SF162ΔV1, remains as resistant to antibody-mediated neutalization as the wild-type virus SF162. In contrast, the mutant virus with the V2 loop deletion, SF162ΔV2, exhibits enhanced susceptibility to neutralization by certain monoclonal antibodies whose epitopes relocated within the CD4-binding site and conserved regions of gp120. More importantly, SF162ΔV2 is now up to 170-fold more susceptible to neutralization than SF162 by sera collected from patients infected with clade B HIV-1 isolates. In addition, it becomes susceptible to neutralization by sera collected from patients infected with clade A, C, D, E, and F HIV-1 isolates. The Examiner asserts that these findings suggest that the V2, but not the V1, loop of SF162 shields an as yet unidentified region of the HIV envelope rich in neutralization epitopes and that the overall structure of this region appears to be conserved among clade B. C. D. E. and F HIV-1 PR isolates. Thus, this teaching provides V2 region deleted HIV-1 viruses (SF162 comprising the same SEQ ID NOS.: set forth in claims 5 and 7). Furthermore, the recombinant envelope set forth in this publication can be neutralized by antisera from different viral clades. This teaching does not disclose methods of immunization against heterologous isolates employing the V2-deleted recombinants. The Examiner alleges that the authors clearly and unambiguously

state (see p. 7844, last paragraph) that "The envelope of SF162ΔV2 could be used as an immunogen to generate antibodies against the exposed region. We believe that such antibodies would have a more potent cross-clade neutralizing potential than antibodies generated against the envelope of SF162." Based on this speculation, the Examiner alleges that it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to immunize a host against heterologous HIV-1 employing the SF162ΔV2 construct described by Stamatatos and Cheng-Mayer since they teach that such an immunogen would have potent cross-clade neutralizing activity and prove more valuable as an immunogen.

As previously set forth, Applicants respectfully traversed this rejection and provided four citations (Kim, et al., 2003: Haigwood, et al., 1990: Bolmstedt, et al., 1996: Lu, et al., 1998) in support of Applicants' position that Stamatatos and Cheng-Mayer do not render the pending claims unpatentable under 35 U.S.C. 103(a) by asserting that these four citations taught away from this reference. Applicants were reminded that the claims are directed toward HIV-1 envelope proteins having a deletion in V2. The Examiner asserted that the references supplied dealt with constructs having deletions in both V1 and V2 (V1/V2), V1-V3 (V1/V3), V3-V5 and V1-V5. The Examiner further asserted that none of these citations provide any data pertaining to HIV-1 envelopes carrying a single deletion in the V2 region, and while these references suggest that deletion of the aforementioned domains fails to generate broadly neutralizing antibodies, none of these publications dealt exclusively with V2 deletions.

The Examiner now alleges that the references relied upon in the rejection clearly demonstrated that V2 deletions are capable of inducing broadly neuturalizing antisera as evidenced by the patient data. Applicants respectfully traverse this assertion and submit that none of these references demonstrated cross-clade neutralizing antibody induction in patients. The Examiner notes that the claims are simply directed toward an HIV-1 envelope comprising a V2 deletion that can induce immunity to at least one other HIV-1 strain, and that none of the claim limitations specify that the claimed invention is capable of inducing cross-clade neutralizing antibody response when used to immunize any given host.

Applicants respectfully traverse the Examiner's present rejection and assert that the claims as currently amended are not unpatentable over the Stamatatos and Cheng-Mayer reference.

The invention as claimed. The currently amended and new claims read on methods of immunizing an animal against heterologous HIV-1 using an immunogen comprising at least one modified HIV-1 envelope protein or fragment thereof, or DNA or viral vector comprising the human CMV enhancer/promoter elements, wherein the leader peptide of the HIV envelope is replaced with a tissue-specific plasminogen activator gene, wherein the vector encodes a modified envelope protein or fragment thereof having a V2 region deletion, and wherein the animal exhibits immunity to at least one HIV-1 strain other than that of said immunogen. In addition, a viral vector comprising the human CMV enhancer/promoter elements is claimed, wherein the leader peptide of the HIV envelope is replaced with a tissue-specific plasminogen activator gene. This vector encodes a modified envelope protein or fragment thereof having a V2 region deletion, and the animal immunized using this vector exhibits immunity to at least one HIV-1 strain other than that of the immunogen. The V2 region deletion comprises deletion of amino acid residues from about T160 through Y189, and the method of immunization results in induction of a cross-clade neutralizing or protective antibody response.

The Stamatatos and Cheng-Mayer reference as a whole. The Stamatatos and Cheng-Mayer reference is an article that demonstrates that deletion of the V2 loop from a clade B HIV-1 isolate results in neutralization of the virus by sera derived from patients infected with clade A, B, C, D, E and F HIV-1 isolates. While the authors propose that the use of the envelope from the virus having the V2 region deletion could be used to generate antibodies against the exposed region, no data is provided to support this theory. Accordingly, the reference is not enabled for such teachings. In particular, Stamatatos and Cheng-Mayer do not prepare antibodies against the envelope proteins derived from the V2 deletion isolate, nor do they provide evidence that antibodies prepared against the envelope proteins from this V2 isolate exhibit broad neutralization properties. Furthermore, Stamatatos and Cheng-Mayer do not demonstrate that antibodies raised

against the envelope proteins from this V2 deletion isolate are protective antibodies. In addition, Stamatatos and Cheng-Mayer do not utilize methods for inducing a heterologous immune response against other HIV virus clades by employing a viral envelope encoded by a vector comprising the human CMV enhancer/promoter elements, wherein the leader peptide of the HIV envelope is replaced with a tissue-specific plasminogen activator gene. They also do not teach or suggest that such a vector as currently claimed in the present application encodes a modified envelope protein or fragment thereof having a V2 region deletion in the region ranging from about T160 through Y189, which when used to immunize an animal results in generation of a cross clade neutralizing antibody response. Nor do they teach or suggest that such a vector as the one taught by the present invention could be codon optimized to achieve increased expression of the modified viral envelope proteins.

The analysis under § 103(a). Stamatatos and Cheng-Mayer do not teach that the clade B isolate having the V2 loop deleted can elicit a broad heterologous humoral immune response including the generation of neutralizing and protective antibodies when administered to animals, as presently claimed in the instant application. Demonstrating neutralization of certain viral isolates, such as the clade B isolate claimed herein, with sera taken from patient samples does not suggest that the same viral isolate, when injected into animals, will elicit a broad heterologous antibody response. Applicants assert that the Stamatatos and Cheng-Mayer reference merely demonstrates that the V2 loop deletion makes the virus more susceptible to serum mediated neutralization, which is not the same as demonstrating that the virus containing the V2 loop deletion is capable of eliciting a broad and heterologous antibody response in vivo.

In addition, Stamatatos and Cheng-Mayer do not teach nor suggest a method for immunizing an animal against heterologous HIV-1 by using a viral vector comprising the human CMV enhancer/promoter elements, wherein the leader peptide of the HIV envelope is replaced with a tissue-specific plasminogen activator gene, and wherein the vector encodes a modified envelope protein or fragment thereof having a V2 region deletion, and wherein the animal exhibits immunity to at least one HIV-1 strain other than that of the immunogen. In the Stamatatos and Cheng-Mayer reference, the viral

construct uses its own promoters. Furthermore, the leader peptide of Stamatatos and Cheng-Mayer was not altered and replaced with a tissue-specific plasminogen activator gene, as was used in the instant application. In addition, Stamatatos and Cheng-Mayer do not teach nor suggest a viral vector comprising the human CMV enhancer/promoter elements, wherein the leader peptide of the HIV envelope is replaced with a tissue-specific plasminogen activator gene, and wherein the vector encodes a modified envelope protein or fragment thereof having a V2 region deletion in the region ranging from about T160 through Y189, and wherein the method of immunization results in induction of a cross-clade neutralizing or protective antibody response. Stamatatos and Cheng-Mayer did not express the gp140 portion of the SF162 and DV2 envelopes using a vector that contains the CMV enhancer promoter elements. Nor did Stamatatos and Cheng-Mayer appreciate the increase in expression of the envelope proteins by replacing the leader peptide with a tissue specific plasminogen activator gene. The improvement in the expression of the viral envelope proteins using this vector construct was not appreciated until the time of the instant application.

Applicant(s) respectfully request withdrawal of the Examiner's rejection for the following reasons. According to the Examiner's assessment, the Stamatatos and Cheng-Mayer reference provides a suggestion to the skilled artisan that the viral envelope having the V2 region deleted would be a target to consider for immunization purposes. However, there is no evidence in the Stamatatos and Cheng-Mayer reference or the extant art, as provided herein, to confirm that such a method would work using the currently claimed methods. As the Examiner will appreciate, the "obvious to try" rationale is insufficient to establish that the skilled artisan was given the required suggestion by the cited reference to arrive at the present invention so that the invention is thereby rendered obvious. There must be objective evidence that the proposed method would work. There is no objective evidence in the cited Stamatatos and Cheng-Mayer reference that leads one skilled in the art to conclude that the methods of the present invention for elicitation of a broad heterologous antibody response would work, and thus would not motivate the skilled artisan to arrive at the present invention. Furthermore, Applicants amendments to the claims have further differentiated the present invention from the Stamatatos and

Cheng-Mayer reference in that the vectors encoding the viral envelope constructs are neither taught nor suggested by Stamatatos and Cheng-Mayer. In particular, Stamatatos and Cheng-Mayer do not teach nor suggest modifications of HIV envelope proteins using a vector whereby the CMV enhancer promoter elements replace the HIV-1 promoter. Nor do Stamatatos and Cheng-Mayer teach or suggest replacement of the leader peptide with a tissue specific plasminogen activator gene in order to provide for higher expression of modified viral envelope proteins. Furthermore, Stamatatos and Cheng-Mayer do not teach nor suggest that such vector construct could achieve higher expression and may lead to more efficient induction of a cross-clade neutralizing antibody response. Only through the Applicant(s) work included in the instant application has the evidence been provided for the superiority of the methods claimed.

Furthermore, obviousness requires a reasonable expectation of success. Applicant(s) respectfully assert that as related to the claims as currently amended, a reasonable expectation for success would be questionable based on the level of skill in the art at the time that the present invention was made. Several investigators tried various means of altering the variable loop domains of HIV-1 in order to generate antibodies with broad heterologous neutralization capability, but have failed. It was not until the time of the present invention that a broad heterologous antibody response was demonstrated using the vectors and modified HIV-1 envelope construct having the V2 loop deletion as currently claimed. It is only through the findings in the present application that success was attained. Accordingly, Applicants respectfully request withdrawal of the rejection.

Fees

A check in the amount of $250 is enclosed herewith to cover the additional new claims. No other fees are believed to be required, but if so, the Commissioner is hereby authorized to charge any fees, or credit any overpayment, to Deposit Account No. 11-1153.

Conclusion

Applicants believe that the claim amendments provided herein put the application in condition for allowance. Withdrawal of the rejections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,

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Attachments: Two interview summaries